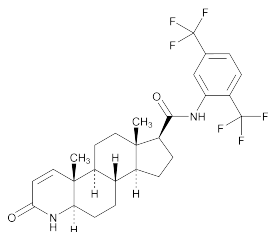


## Dutasteride



$C_{27}H_{30}F_6N_2O_2$  528.53  
(5 $\alpha$ ,17 $\beta$ )-N-[2,5-Bis(trifluoromethyl)phenyl]-3-oxo-4-azaandroster-1-ene-17-carboxamide;  
 $\alpha,\alpha,\alpha,\alpha',\alpha'$ -Hexafluoro-3-oxo-4-aza-5 $\alpha$ -androst-1-ene-17 $\beta$ -carboxy-2',5'-xylylide [164656-23-9].

### DEFINITION

Dutasteride contains NLT 97.0% and NMT 102.0% of dutasteride ( $C_{27}H_{30}F_6N_2O_2$ ), calculated on the anhydrous and solvent-free basis.

### IDENTIFICATION

#### Change to read:

- **A. INFRARED ABSORPTION** (197K) or (197M). • (197A) may be used. • (IRA 1-Mar-2016)
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

### ASSAY

#### PROCEDURE

**Diluent:** Acetonitrile and water (60:40)

**Mobile phase:** Acetonitrile, water, and trifluoroacetic acid (52: 48: 0.025)

**System suitability solution:** 0.5 mg/mL of USP Dutasteride Resolution Mixture RS in *Diluent*. Sonicate to dissolve.

**Standard solution:** 0.5 mg/mL of USP Dutasteride RS in *Diluent*. Sonicate to dissolve.

**Sample solution:** 0.5 mg/mL of Dutasteride in *Diluent*. Sonicate to dissolve.

**Chromatographic system**  
(See *Chromatography* (621), *System Suitability*.)

**Mode:** LC

**Detector:** UV 220 nm

**Column:** 4.6-mm  $\times$  25-cm; 5- $\mu$ m packing L1

**Column temperature:** 35 $^{\circ}$

**Flow rate:** 1 mL/min

**Injection volume:** 10  $\mu$ L

**Run time:** 1.5 times the retention time of dutasteride

#### System suitability

**Samples:** *System suitability solution* and *Standard solution*

[NOTE—See *Table 3* for the relative retention times.]

#### Suitability requirements

**Resolution:** NLT 1.5 between dutasteride 17 $\alpha$ -epimer and dutasteride, *System suitability solution*

**Relative standard deviation:** NMT 1.5%, *Standard solution*

#### Analysis

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of dutasteride ( $C_{27}H_{30}F_6N_2O_2$ ) in the portion of Dutasteride taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

$r_U$  = peak response from the *Sample solution*  
 $r_S$  = peak response from the *Standard solution*  
 $C_S$  = concentration of USP Dutasteride RS in the *Standard solution* (mg/mL)  
 $C_U$  = concentration of Dutasteride in the *Sample solution* (mg/mL)

**Acceptance criteria:** 97.0%–102.0% on the anhydrous and solvent-free basis

### IMPURITIES

- **RESIDUE ON IGNITION** (281): NMT 0.1%

#### Change to read:

#### LIMIT OF PLATINUM

[NOTE—Perform this test only if platinum is a known inorganic impurity of the manufacturing process.]

**Diluent:** Hydrochloric acid and dimethyl sulfoxide (2:98). Prepare in a plastic volumetric flask.

**Standard stock solution:** 10  $\mu$ g/mL of platinum in *Diluent*. Prepare by diluting (1:100) a 1000- $\mu$ g/mL commercially available platinum standard.

**Standard solution 1:** 1.0  $\mu$ g/mL of platinum in *Diluent* from the *Standard stock solution*

**Standard solution 2:** 0.1  $\mu$ g/mL of platinum in *Diluent* from *Standard solution 1*

**Sample solution:** 0.01 g/mL of Dutasteride in *Diluent*. Sonicate to dissolve.

#### Instrumental conditions

(See *Plasma Spectrochemistry* (730).)

**Mode:** ICP–OES

**Analytical wavelength:** 306.471 nm

**Spectrophotometric system:** Use an inductively coupled plasma–optical emission spectrophotometric system, and construct a calibration curve using the response from the *Diluent*, *Standard solution 1*, and *Standard solution 2*.

#### System suitability

**Samples:** *Diluent*, *Standard solution 1*, and *Standard solution 2*

#### Suitability requirements

**Limit of quantitation:** 3  $\mu$ g/g for platinum. • (IRA 1-Mar-2016)

Calculate the limit of quantitation from the *Diluent*:

$$\text{Result} = 10 \times (SD/C_S)$$

$SD$  = standard deviation of platinum from *Diluent* ( $\mu$ g/mL)

$C_S$  = nominal concentration of • dutasteride • (IRA 1-Mar-2016) in the *Sample solution* (g/mL)

**Correlation coefficient:** NLT 0.99 from the *Diluent*, *Standard solution 1*, and *Standard solution 2*

#### Analysis

**Samples:** *Diluent*, *Standard solution 1*, *Standard solution 2*, and *Sample solution*

Plot the responses of the *Diluent*, *Standard solution 1*, and *Standard solution 2* versus their content (0, 0.1, and 1.0  $\mu$ g/mL) of platinum. Determine the concentration, in  $\mu$ g/mL, of platinum in the *Sample solution* from the calibration curve.

Calculate the concentration, in  $\mu$ g/g, of platinum in the portion of Dutasteride taken:

$$\text{Result} = C_S/C_U$$

$C_S$  = concentration of platinum in the *Sample solution* ( $\mu$ g/mL)

$C_U$  = concentration of Dutasteride in the *Sample solution* (g/mL)

## 2 Dutasteride

Acceptance criteria: NMT 5 µg/g

• **LIMIT OF RESIDUAL SOLVENTS**

**Standard stock solution:** 5 mg/mL each of acetonitrile, ethyl acetate, pyridine, toluene, dioxane, and *n*-heptane in dimethyl sulfoxide

**Standard solution:** 10 µg/mL each of acetonitrile, ethyl acetate, pyridine, toluene, dioxane, and *n*-heptane in dimethyl sulfoxide from the *Standard stock solution*

**Sample solution:** 10 mg/mL of Dutasteride in dimethyl sulfoxide

**Chromatographic system**

(See *Chromatography* (621), *System Suitability*.)

**Mode:** GC

**Detector:** Flame ionization

**Column:** 0.32-mm × 30-m; capillary coated with 5-µm film of G1

**Temperatures**

**Injection port:** 180°

**Detector:** 260°

**Column:** See *Table 1*.

**Table 1**

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
50	—	50	3
50	10	200	2

**Carrier gas:** Helium

**Flow rate:** Head pressure at 12 psi

**Split flow:** 10 mL/min

**Septum purge:** 2 mL/min

**Injector type:** Headspace

**Sample volume:** 2 mL

**Temperatures**

**Sample:** 85°

**Needle:** 100°

**Transfer line:** 110°

**Times**

**Equilibration:** 1 min

**Thermostating:** 15 min

**System suitability**

**Sample:** *Standard solution*

**Suitability requirements**

**Resolution:** NLT 1.2 between *n*-heptane and dioxane peaks

**Relative standard deviation:** NMT 5% for each solvent

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of each solvent in the portion of Dutasteride taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

$r_U$  = peak response of each solvent from the *Sample solution*

$r_S$  = peak response of each solvent from the *Standard solution*

$C_S$  = concentration of each solvent in the *Standard solution* (mg/mL)

$C_U$  = concentration of Dutasteride in the *Sample solution* (mg/mL)

**Acceptance criteria:** See *Table 2*.

**Table 2**

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Acetonitrile	0.30	0.3
Ethyl acetate	0.60	0.2
Dioxane	0.83	0.1
<i>n</i> -Heptane	0.85	0.5
Pyridine	0.92	0.2
Toluene	1.0	0.2

**Change to read:**

• **ORGANIC IMPURITIES, PROCEDURE 1**

**Diluent, Mobile phase, System suitability solution, Sample solution, and Chromatographic system:** Proceed as directed in the *Assay*.

**System suitability**

**Sample:** *System suitability solution*

[NOTE—See *Table 3* for the relative retention times.]

**Suitability requirements**

**Resolution:** NLT 1.5 between dutasteride 17 $\alpha$ -epimer and dutasteride

**Analysis**

**Sample:** *Sample solution*

Calculate the percentage of each impurity in the portion of Dutasteride taken:

$$\text{Result} = (r_U/r_T) \times (1/F) \times 100$$

$r_U$  = peak area for each impurity from the *Sample solution*

$r_T$  = sum of the peak areas from the *Sample solution*

$F$  = relative response factor (see *Table 3*)

**Acceptance criteria:** See *Table 3*.

• **Table 3**

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Dutasteride acid <sup>a</sup>	0.10	1.0	0.2
Dutasteride dimethylamide <sup>b</sup>	0.11	1.4	0.2
Dutasteride methyl ester <sup>c</sup>	0.28	1.0	0.15
Dutasteride ethyl ester <sup>d</sup>	0.39	1.0	0.2
Dutasteride 17 $\alpha$ -5-ene <sup>e</sup>	0.90	1.0	0.2
Dutasteride 17 $\alpha$ -epimer	0.93	1.0	0.3
Dutasteride	1.00	—	—
Chlorodutasteride <sup>f</sup>	1.15	0.33	0.4

<sup>a</sup> (5 $\alpha$ ,17 $\beta$ )-3-Oxo-4-azaandrost-1-ene-17-carboxylic acid.

<sup>b</sup> (5 $\alpha$ ,17 $\beta$ )-*N,N*-Dimethyl-3-oxo-4-azaandrost-1-ene-17-carboxamide.

<sup>c</sup> Methyl (5 $\alpha$ ,17 $\beta$ )-3-oxo-4-azaandrost-1-ene-17-carboxylate.

<sup>d</sup> Ethyl (5 $\alpha$ ,17 $\beta$ )-3-oxo-4-azaandrost-1-ene-17-carboxylate.

<sup>e</sup> (17 $\alpha$ )-*N*-[2,5-Bis(trifluoromethyl)phenyl]-3-oxo-4-azaandrost-1,5(6)-diene-17-carboxamide.

<sup>f</sup> (1 $\alpha$ ,5 $\alpha$ ,17 $\beta$ )-*N*-[2,5-Bis(trifluoromethyl)phenyl]-1-chloro-3-oxo-4-azaandrostane-17-carboxamide.

<sup>g</sup> (17 $\beta$ )-*N*-[2,5-Bis(trifluoromethyl)phenyl]-3-oxo-4-azaandrost-1,5(6)-diene-17-carboxamide.

Table 3 (Continued)

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Dutasteride 5-enes	1.20	1.0	0.3
Any other individual impurity	—	—	0.1

- <sup>a</sup> (5 $\alpha$ ,17 $\beta$ )-3-Oxo-4-azaandrost-1-ene-17-carboxylic acid.  
<sup>b</sup> (5 $\alpha$ ,17 $\beta$ )-N,N-Dimethyl-3-oxo-4-azaandrost-1-ene-17-carboxamide.  
<sup>c</sup> Methyl (5 $\alpha$ ,17 $\beta$ )-3-oxo-4-azaandrost-1-ene-17-carboxylate.  
<sup>d</sup> Ethyl (5 $\alpha$ ,17 $\beta$ )-3-oxo-4-azaandrost-1-ene-17-carboxylate.  
<sup>e</sup> (17 $\alpha$ )-N-[2,5-Bis(trifluoromethyl)phenyl]-3-oxo-4-azaandrost-1,5(6)-diene-17-carboxamide.  
<sup>f</sup> (1 $\alpha$ ,5 $\alpha$ ,17 $\beta$ )-N-[2,5-Bis(trifluoromethyl)phenyl]-1-chloro-3-oxo-4-azaandrostane-17-carboxamide.  
<sup>g</sup> (17 $\beta$ )-N-[2,5-Bis(trifluoromethyl)phenyl]-3-oxo-4-azaandrost-1,5(6)-diene-17-carboxamide.

● (IRA 1-Mar-2016)

**Change to read:**

● **ORGANIC IMPURITIES, PROCEDURE 2**

**Diluent, System suitability solution, and Sample solution:** Prepare as directed in the Assay.

**Mobile phase:** Acetonitrile and water (80:20)

**Chromatographic system**

(See Chromatography <621>, System Suitability.)

**Mode:** LC

**Detector:** UV 220 nm

**Column:** 4.6-mm  $\times$  15-cm; 5- $\mu$ m packing L11

**Flow rate:** 1 mL/min

**Injection volume:** 10  $\mu$ L

**Run time:** 5 times the retention time of dutasteride

**System suitability**

**Sample:** System suitability solution

**Suitability requirements**

**Resolution:** NLT  $\bullet$  1.5 $\bullet$  (IRA 1-Mar-2016) between dutasteride  $\alpha$ -dimer and dutasteride  $\beta$ -dimer peaks

**Analysis**

**Sample:** Sample solution

Integrate the dutasteride peak and all drug-related peaks eluting after the dutasteride peak.

Calculate the percentage of each impurity in the portion of Dutasteride taken:

$$\bullet \text{Result} = (r_U/r_T) \times (1/F) \times 100 \bullet \text{ (IRA 1-Mar-2016)}$$

$r_U$  = peak area of each impurity from the Sample solution

$r_T$  = sum of the peak areas from the Sample solution

$\bullet F$  = relative response factor (see Table 4) $\bullet$  (IRA 1-Mar-2016)

**Acceptance criteria:** See Table 4.

Table 4

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Dutasteride	1.0	—	—
Dihydrodutasteride <sup>a</sup>	1.19	0.38	0.15
Dutasteride $\alpha$ -dimer	3.7	1.0	0.3
Dutasteride $\beta$ -dimer	4.3	1.0	0.5
Any other individual impurity	—	—	0.1
Total impurities <sup>b</sup>	—	—	2.0

<sup>a</sup> (5 $\alpha$ ,17 $\beta$ )-N-[2,5-Bis(trifluoromethyl)phenyl]-3-oxo-4-azaandrost-17-carboxamide.

<sup>b</sup> Sum of impurities from Table 3 and Table 4.

● (IRA 1-Mar-2016)

**SPECIFIC TESTS**

**Change to read:**

● **WATER DETERMINATION** <921>, Method 1c

**Sample:** 100 mg

**Analysis:**  $\bullet$ The Sample is heated in a tube at 180 $^\circ$  for 4 min in a stream of dry inert gas. $\bullet$  (IRA 1-Mar-2016)

**Acceptance criteria:** NMT 0.50%

● **OPTICAL ROTATION** <781S>, Procedures, Specific Rotation

**Sample solution:** 10 mg/mL in chloroform and alcohol (98:2)

**Acceptance criteria:** +15.0 $^\circ$  to +25.0 $^\circ$

**ADDITIONAL REQUIREMENTS**

● **PACKAGING AND STORAGE:** Preserve in tight containers, and store below 30 $^\circ$ .

**Change to read:**

● **USP REFERENCE STANDARDS** <11>

USP Dutasteride RS

USP Dutasteride Resolution Mixture RS

The mixture contains  $\bullet$ Dutasteride and $\bullet$  (IRA 1-Mar-2016) the following impurities (other impurities may also be present):

Dutasteride 17 $\alpha$ -epimer: (5 $\alpha$ ,17 $\alpha$ )-N-[2,5-Bis(trifluoromethyl)phenyl]-3-oxo-4-azaandrost-1-ene-17-carboxamide.

C<sub>27</sub>H<sub>30</sub>F<sub>6</sub>N<sub>2</sub>O<sub>2</sub> 528.53

Dutasteride  $\alpha$ -dimer: {[ (5 $\alpha$ ,17 $\beta$ )-N-[2,5-Bis(trifluoromethyl)phenyl]-3-oxo-4-azaandrost-1-ene-17-carboxamide-]4-yl} {[ (5 $\alpha$ ,17 $\alpha$ )-3-oxo-4-azaandrost-1-ene]-17-yl}methanone.

C<sub>46</sub>H<sub>55</sub>F<sub>6</sub>N<sub>3</sub>O<sub>4</sub> 827.94

Dutasteride  $\beta$ -dimer: {[ (5 $\alpha$ ,17 $\beta$ )-N-[2,5-Bis(trifluoromethyl)phenyl]-3-oxo-4-azaandrost-1-ene-17-carboxamide-]4-yl} {[ (5 $\alpha$ ,17 $\beta$ )-3-oxo-4-azaandrost-1-ene]-17-yl}methanone.

C<sub>46</sub>H<sub>55</sub>F<sub>6</sub>N<sub>3</sub>O<sub>4</sub> 827.94